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Relative Contribution of Lipids and Apolipoproteins to Incident Coronary Heart Disease and Ischemic Stroke: The PRIME Study

Florence Canoui-Poitrine^{a, b} Gerald Luc^c Jean-Marie Bard^d Jean Ferrieres^e
John Yarnell^j Dominique Arveiler^f Pierre Morange^g Frank Kee^j Alun Evans^j
Philippe Amouyel^h Pierre Ducimetiereⁱ Jean-Philippe Empana^a
on behalf of the PRIME Study Group

^aINSERM, U970, Paris Cardiovascular Research Center, Université Paris Descartes, UMR-S970, Paris,

^bHospices Civils de Lyon, Pôle Information Médicale Evaluation Recherche, Université Lyon 1, Lyon,

^cDepartment of Atherosclerosis, INSERM, U545, Institut Pasteur de Lille, Lille 2 University, Lille,

^dFaculté de Pharmacie, Université de Nantes, Nantes, ^eThe Toulouse MONICA Project, INSERM, U558,

Département d'Epidémiologie, Université Paul Sabatier, Toulouse, ^fThe Strasbourg MONICA Project,

Laboratoire d'Epidémiologie et de Santé Publique, EA 3430, and Université de Strasbourg, Strasbourg,

^gINSERM, U626, Laboratory of Hematology, La Timone Hospital, Marseille, ^hThe Lille MONICA Project, INSERM,

U744, Institut Pasteur de Lille, Université Lille Nord de France, Lille, and ⁱINSERM, Université Paris Sud-XI,

Paris, France; ^jThe UKCRC Center of Excellence for Public Health, The Queen's University, Belfast, UK

Key Words

Epidemiology · Coronary heart disease · Ischemic stroke · Risk factors · Lipids

Abstract

Aim: To compare within the same cohort the association of a large panel of lipids with the risk of incident coronary heart disease (CHD) and ischemic stroke events in participants of the Prospective Epidemiological Study of Myocardial Infarction. **Methods:** In this binational (Northern Ireland and France) prospective cohort, we considered 9,711 men aged 50–59 years free of CHD and stroke at baseline (1991–1993). The hazard ratios of each lipid marker for CHD and ischemic stroke events were estimated in separate Cox proportional hazard models adjusted for age, study center, systolic blood pressure, antihypertensive treatment, current smoking sta-

tus, body mass index and diabetes. **Results:** After 10 years of follow-up, 635 men had a first CHD and 98 a first ischemic stroke event. Total cholesterol (total-C), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), non-HDL-C, triglycerides, apolipoprotein (Apo) A1 and Apo B100, their ratios and lipoprotein (a) [Lp(a)] were all significantly predictive of future CHD. Associations with ischemic stroke followed the same trend as for CHD, but with lower strength, and none were statistically significant. However, none of the differences between the hazard ratios for CHD and for ischemic stroke were statistically significant. **Conclusions:** In healthy, middle-aged men, total-C, HDL-C, LDL-C, non-HDL-C, triglycerides, Apo A1 and Apo B100, their ratios and Lp(a) are, if anything, weak predictors of ischemic stroke events over a 10-year period.

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Introduction

Several large randomized controlled trials have shown that cholesterol-lowering statin therapy can significantly reduce the risk of both coronary heart disease (CHD) and ischemic stroke [1–4]. While the link between lipids and CHD risk is firmly established [5–7], it is still unclear whether there is one between lipids and ischemic stroke [8]. An association between lipids and ischemic stroke has been supported by some [9–12] but not all observational studies [13–17], suggesting an apparent stroke paradox for lipids [18]. To date, only one cohort study has jointly evaluated the association of several lipids with future CHD and ischemic stroke events and has suggested that lipids were also predictive of future ischemic stroke but with lower strength compared to CHD. However, this study was conducted in women only [10]. Therefore, we aimed to extend this previous analysis to compare, within the same cohort of European, middle-aged, male participants of the Prospective Epidemiological Study of Myocardial Infarction (PRIME), the relative contribution of a large panel of circulating lipid markers to the occurrence of CHD and ischemic stroke events as the first presentation of cardiovascular disease.

Methods

Study Population

The PRIME Study is a multicenter prospective cohort study designed to identify risk factors for CHD. Details of recruitment and the baseline examination of the PRIME Study have been described previously [19]. The target study size was to recruit 2,500 men aged 50–59 years in each of the 4 collaborating World Health Organization (WHO) Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) centers in Belfast (Northern Ireland), Lille, Strasbourg and Toulouse (France). Overall, 10,602 men aged 50–59 years were recruited between 1991 and 1993. Among them, 823 had coronary disease and 77 a history of stroke at baseline examination and were excluded from the present analysis, leaving a study population of 9,711 men (7,319 in France and 2,392 in Northern Ireland).

Baseline Examination

General Characteristics

Subjects who agreed to participate in the study were given a morning appointment and asked to fast for at least 12 h. A full description of clinical and laboratory measurements has been published elsewhere [19]. Briefly, a self-administered health questionnaire was completed by subjects at their home and was subsequently checked by trained interviewers at the clinic. It covered a broad range of clinical information including family and personal clinical history using the Rose Questionnaire, alcohol consumption, cigarette smoking and medication use. Diabetes was defined as the current intake of oral hypoglycemic treatment or

use of insulin. Blood pressure was measured with the patient in the sitting position using the same automatic device (Spengler SP9, Spengler, Cachan, France). A 12-lead electrocardiogram was also recorded.

Biological Measurements

A subset of biological measurements was performed in the entire cohort at baseline after overnight fasting. Plasma lipid analyses were centralized (SERLIA INSERM U325, Institut Pasteur de Lille, France). Total cholesterol (total-C) was measured by enzymatic methods using commercial kits in an automatic analyzer (Boehringer, Mannheim, Germany). High-density lipoprotein cholesterol (HDL-C) was determined by enzymatic methods (Boehringer) after precipitation of apolipoprotein B-containing lipoproteins. Low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald formula for triglycerides ≤ 4.5 g/l. Non-HDL-C was calculated using the following equation: non-HDL-C = total-C – HDL-C. Apolipoprotein (Apo) A1 and Apo B100 were quantified using commercial reagent immunonephelometry (Behringwerke, Marburg, Germany). Lipoprotein (a) [Lp(a)] was measured by a selective bi-site immunoenzymatic assay as previously described [20].

The number of men with missing lipid measurements was as follows: total-C, $n = 44$ (0.45%); HDL-C, $n = 47$ (0.48%); Apo A1, $n = 45$ (0.46%); Apo B100, $n = 45$ (0.47%), and Lp(a), $n = 50$ (0.51%).

Follow-Up and Ascertainment of Cases

During the 10-year follow-up, subjects were contacted annually by letter and asked to complete a clinical event questionnaire. For all subjects who reported a possible event, clinical information was sought directly from the hospital or general practitioner records. All details of electrocardiograms, computerized tomodensitometry scans, hospital admissions, cardiac enzymes, surgical intervention, angioplasty, angiography and treatments were collected. For deceased patients, the circumstances of death were obtained from the practitioner or the family whenever possible. In the few cases where the circumstances surrounding the death were not available from the practitioner or the family, death certificates were checked for supporting clinical and postmortem information on the cause of death.

Incident CHD and ischemic stroke events were validated by two independent medical committees. CHD events (stable and unstable angina, myocardial infarction and coronary death) were defined as previously described using clinical, biological, stress test, scintigraphic or angiographic criteria [19].

Stroke was defined according to the WHO MONICA criteria [21] as a new focal or global neurologic deficit of rapid onset and of vascular origin that persisted for more than 24 h (except if the symptoms were interrupted by a surgical intervention or a death). Transient ischemic attacks and strokes caused by a blood disease, a cerebral tumor or metastasis or secondary to a trauma were not considered by the stroke medical committee.

Clinical information, computerized tomodensitometry scans (compatible signs) and angiographic and autopsy data were used to evaluate and distinguish ischemic from hemorrhagic (subarachnoid or intracerebral hemorrhage) stroke events. After 10 years of follow-up, the CHD and ischemic stroke event status was available for 95.1% of the cohort. The 4.9% of men with unknown CHD and ischemic stroke event status had lower total-C, LDL-C, HDL-C and Apo A1 levels, higher Lp(a) and body mass index and

Table 1. Baseline non-lipid risk factors according to the clinical event developed during 10 years of follow-up in the PRIME Study

	No incident clinical event (n = 8,978)	CHD (n = 635)	Ischemic stroke (n = 98)	p value
Age, years	54.8 ± 2.88	55.3 ± 2.93	55.6 ± 3.01	<0.001
Current smoker, %	26.8 (2,410)	36.4 (231)	40.8 (40)	<0.001
Systolic blood pressure, mm Hg	133.0 ± 18.5	140.8 ± 21.1	142.5 ± 22.3	<0.001
Diastolic blood pressure, mm Hg	83.5 ± 11.5	87.0 ± 12.5	87.0 ± 14.0	<0.001
Antihypertensive treatment, %	8.8 (761)	15.5 (92)	17.4 (16)	<0.001
Aspirin, %	3.4 (308)	2.3 (15)	2.0 (2)	0.23
Body mass index	26.5 ± 3.4	27.3 ± 3.6	26.9 ± 4.0	<0.001
Diabetes, %	2.0 (180)	4.4 (28)	9.2 (9)	<0.001

Data are means ± SD and percentages (numbers in parentheses) for continuous and categorical variables, respectively. p values are the results of global comparison across the 3 groups using Pearson χ^2 test and ANOVA for categorical and continuous variables, respectively.

were more frequently current smokers compared to those in whom the status was known.

The study protocol was approved by the institutional review board of Broussais Hospital, Paris, France. Informed consent was obtained for each man who agreed to participate in the PRIME Study.

Statistical Analysis

Baseline characteristics in the groups of men who remained free of CHD or ischemic stroke events during the follow-up, men who developed a CHD event and men who developed an ischemic stroke event were compared using Pearson χ^2 tests for categorical variables and ANOVA or the Kruskal-Wallis test for continuous variables, as appropriate. To account for multiple testing (n = 12 comparisons of lipid risk factors), a Bonferroni correction was applied and a p value <0.004 indicated a statistically significant difference. Post hoc pair-wise comparisons of lipid risk factors between men who developed a CHD event and men who developed an ischemic stroke event were performed using the Scheffé test. The associations of each lipid parameter with future CHD and ischemic stroke were estimated in separate Cox proportional hazards models. Hazard ratios and their 95% confidence intervals (CIs) were given for 1 SD increase in the lipids calculated in men who remained free of clinical events during the follow-up. Analysis was systematically adjusted for study center, age, systolic blood pressure, antihypertensive treatment, current smoking status, body mass index and diabetes on an a priori basis. For the 20 men who suffered from both a CHD and an ischemic stroke event during follow-up, only the first event was considered for analysis; this group consisted of 12 men with first CHD events and 8 with first ischemic stroke events, respectively. In fact, when the occurrence of a stroke event prior to a CHD event or vice versa was taken into account using the competing risk method (the data-augmented method) [22], similar results were obtained. All comparisons were two-sided. All statistical analyses were performed using Stata software version 9.1™ (StataCorp, College Station, Tex., USA).

Results

The mean age of the 9,711 men was 54.7 ± 2.9 years. After 10 years of follow-up, 635 men had a first CHD event (408 in France and 227 in Northern Ireland) and 122 had a first stroke, including 98 of ischemic origin (64 in France and 34 in Northern Ireland), 18 of hemorrhagic origin and 6 of undetermined origin. First CHD and ischemic stroke occurred a median of 5.0 years (interquartile range 2.8–7.8) and 5.4 years (interquartile range 2.7–7.6), respectively, after baseline examination.

Table 1 compares the non-lipid characteristics of those men who remained free of CHD and ischemic stroke (n = 8,978), those who developed a CHD event (n = 635) and those who had an ischemic stroke event (n = 98) during follow-up. As expected, men who had a clinical event (CHD or ischemic stroke) had a significantly worse cardiovascular risk profile than those who remained free of clinical events. Diabetes was twice as frequent in men with future ischemic stroke as in men with future CHD (p = 0.045). The mean systolic blood pressure (p = 0.48), antihypertensive treatment use (p = 0.65) and aspirin use (p = 0.85) were not statistically different between those with future ischemic stroke and those with future CHD.

Table 2 compares the mean levels of single lipids, lipid ratios and lipid-lowering treatment use between the 3 groups defined above using a Bonferroni correction that accounted for multiple testing. Whereas the proportion of men on lipid-lowering treatment, and statins in particular, did not differ between the groups, lipid levels were on average significantly higher in men who developed

Table 2. Baseline levels of lipid markers, lipid ratios and lipid-lowering treatment use according to the clinical event developed during the 10 years of follow-up in the PRIME Study

	No incident clinical event (n = 8,978)	CHD (n = 635)	Ischemic stroke (n = 98)	p value ¹	p value ²
Total-C, g/l	2.21 ± 0.38	2.33 ± 0.39	2.27 ± 0.41	<0.001	0.30
HDL-C, g/l	0.49 ± 0.13	0.45 ± 0.12	0.48 ± 0.13	<0.001	0.11
LDL-C, g/l	1.43 ± 0.33	1.54 ± 0.35	1.48 ± 0.37	<0.001	0.25
Non-HDL-C, g/l	1.72 ± 0.38	1.88 ± 0.40	1.79 ± 0.44	<0.001	0.08
Apo A1, g/l	1.50 ± 0.25	1.42 ± 0.23	1.46 ± 0.23	<0.001	0.28
Apo B100, g/l	1.26 ± 0.33	1.41 ± 0.37	1.33 ± 0.35	<0.001	0.08
Median Lp(a), mg/dl (25th–75th percentile)	6.5 (2.1–20)	9.8 (3–30)	6.6 (1.7–20)	<0.001	0.073
Triglycerides, g/l	1.46 ± 1.0	1.76 ± 1.16	1.70 ± 1.09	<0.001	0.72
Total-C/HDL-C ratio	4.80 ± 1.54	5.54 ± 1.69	5.13 ± 1.78	<0.001	0.052
LDL-C/HDL-C ratio	3.11 ± 1.13	3.64 ± 1.30	3.34 ± 1.38	<0.001	0.065
Apo B100/Apo A1 ratio	0.87 ± 0.27	1.02 ± 0.31	0.94 ± 0.31	<0.001	0.021
Apo B100/HDL-C ratio	2.82 ± 1.32	3.44 ± 1.49	3.12 ± 1.48	<0.001	0.08
Lipid-lowering treatment, %	8.4 (750)	9.8 (62)	9.2 (9)	0.45	–

Except for Lp(a), data are means ± SD and percentages (numbers in parentheses) for continuous and categorical variables, respectively.

¹ Global comparison across the 3 groups using Pearson χ^2 test and ANOVA or the Kruskal-Wallis test for categorical and continuous variables, respectively; a Bonferroni correction was applied and a p value <0.004 indicated a statistically significant difference.

² Post hoc pair-wise comparisons between men with CHD and men with ischemic stroke events using the Scheffé test. Triglycerides were log-transformed for statistical analysis.

CHD or ischemic stroke compared to those who did not experience an incident clinical event. Moreover, the mean level of non-HDL-C, Apo B100, Lp(a) and each lipid ratio was higher and that of HDL-C lower in men with future CHD than in men with future ischemic stroke events, although the difference was statistically significant for the Apo B100 to Apo A1 ratio only.

The multivariate associations of total-C, HDL-C, LDL-C, non-HDL-C, triglycerides, Apo A1, Apo B100 and Lp(a) with future CHD and ischemic stroke are shown in figure 1. These lipids were all highly predictive of CHD, with comparable magnitude. Associations with ischemic stroke followed the same trend as for CHD, but were of lower strength, and none were statistically significant. However, formal comparison between the hazard ratios for CHD and ischemic stroke did not reach statistical significance.

The multivariate associations of lipid ratios, including total-C/HDL-C, LDL-C/HDL-C, Apo B100/Apo A1 and Apo B100/HDL-C, with CHD and ischemic stroke events are shown in figure 2. As for single lipids, lipid ratios were all predictive of CHD, and the associations were of comparable magnitude. None of the studied lipid ratios was significantly associated with ischemic stroke events. The

magnitude of their association with ischemic stroke was smaller than that for CHD. As for single lipids, however, none of the pair-wise comparisons between the hazard ratios for CHD and for ischemic stroke reached statistical significance. Further adjustment for baseline lipid-lowering treatment did not substantially change the results of the multivariate analyses reported in figures 1 and 2 (not shown). Among the non-lipid cardiovascular risk factors, systolic blood pressure, current smoking status and diabetes were the other independent predictors of ischemic stroke. For instance, in a model evaluating the predictive value of total-C, the corresponding hazard ratios were 1.42 (95% CI 1.16–1.73; p = 0.001) for 1 SD increase in systolic blood pressure, 1.86 (95% CI 1.10–3.12; p = 0.02) for current smoking and 4.59 (95% CI 2.18–9.67; p < 0.001) for diabetes.

Additional Analyses

In the PRIME Study, there was an attempt to classify incident ischemic stroke by subtypes. The 98 first ischemic stroke events included 39 lacunar infarctions, 27 cardioembolic infarctions, 14 atherothrombotic infarctions and 18 nonlacunar, noncardioembolic and nonatherothrombotic infarctions. In a sensitivity analysis in

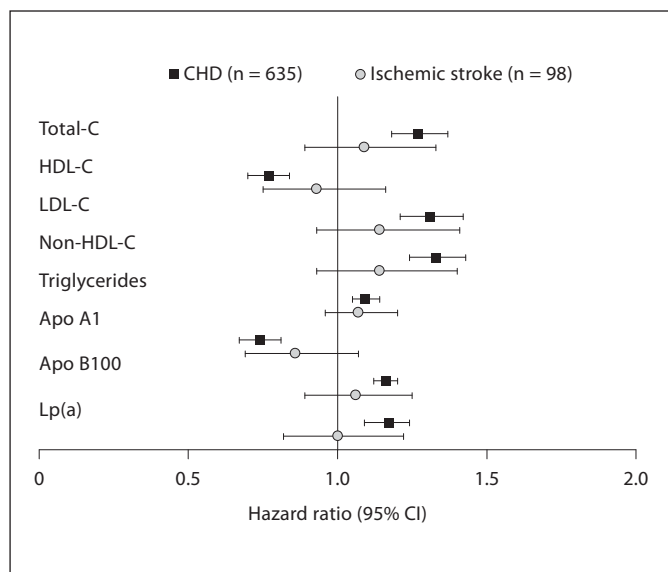


Fig. 1. Standardized adjusted hazard ratios and 95% CIs of single lipids for CHD and ischemic stroke. Hazard ratios of each lipid variable were estimated in separate Cox proportional hazard regression models adjusted for study center, age, systolic blood pressure, antihypertensive treatment, body mass index, diabetes and smoking status. Triglycerides were log-transformed.

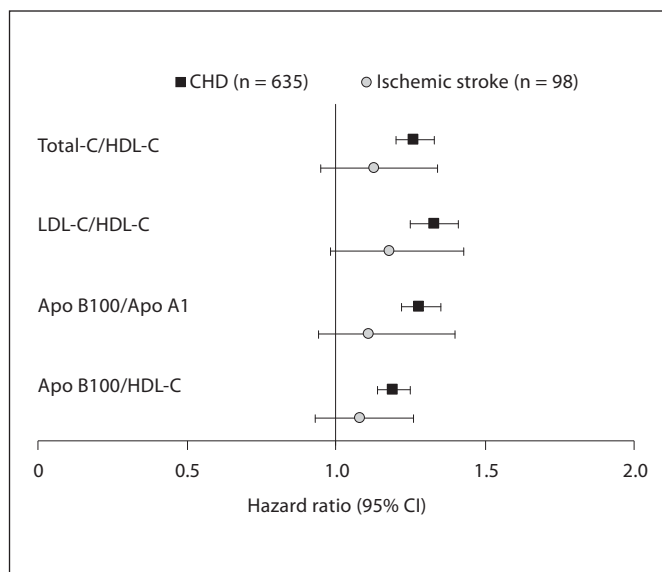


Fig. 2. Standardized adjusted hazard ratios and 95% CIs of lipid ratios for CHD and ischemic stroke. Hazard ratios of each lipid variable were estimated in separate Cox proportional hazard regression models adjusted for study center, age, systolic blood pressure, antihypertensive treatment, body mass index, diabetes and smoking status.

which cardioembolic strokes were excluded (lipids may not be related to this subtype), there was still no significant association between lipids and ischemic stroke in Cox models adjusted for age, study center and systolic blood pressure (not shown).

Discussion

The present population-based study of healthy European middle-aged men suggested that total-C, HDL-C, LDL-C, non-HDL-C, triglycerides, Apo A1 and Apo B100, their ratios and Lp(a) were weak predictors of ischemic stroke events over 10 years compared to their robust association with CHD events. However, it should be noted that none of the differences between the hazard ratios of lipids for CHD and for ischemic stroke was statistically significant.

The strong association between lipids and CHD in the current study is consistent with the well-established link between lipids and CHD [5–7]. There is an ongoing debate as to which lipid variables are the best predictors of future CHD. Apolipoproteins and the Apo B100/Apo A1

ratio have been advocated recently in some [23, 24] but not all studies [25, 26]. In our study, single lipids and apolipoproteins and their corresponding ratios were associated with CHD, with the same order of magnitude over 10 years.

Most previous observational studies have investigated the association between 1 or 2 single lipid markers and ischemic stroke and have reported mixed results. Independent associations were found in a prospective Korean cohort [9] and in a US case-control study [12], but not in 4 large population-based prospective studies [14–17]. Furthermore, in 2 recent meta-analyses of individual data, a weak positive association between total-C and ischemic stroke mortality was found only in the middle-aged subjects (40–59 years) or in those who were normotensive [5], while no association was observed between HDL-C and incident stroke of any type in Asians [27].

To date, only one study conducted in US participants in the Women's Health Study (WHS) has assessed the contribution of a large panel of lipids to both incident ischemic stroke and CHD events [10]. In that study, including 15,632 healthy women, of whom 132 developed

a first ischemic stroke over 10 years of follow-up, total-C, HDL-C, non-HDL-C and LDL-C/HDL-C and total-C/HDL-C ratios were predictive of ischemic stroke, whereas LDL-C, Apo A1, Apo B 100 and Apo B100/HDL-C and Apo B100/Apo A1 ratios were not. The associations with ischemic stroke were weaker than those for CHD risk.

We have complemented the results of the WHS by conducting an analysis in men and by additionally investigating Lp(a). Consistent with the results of the WHS, we found that associations between lipids and ischemic stroke followed the same trend as those for CHD but were of lower magnitude. Contrary to the above study, however, none of the lipids investigated in our study were significantly associated with ischemic stroke. Three main factors may explain why we failed to observe any significant association between lipids and incident ischemic stroke events in the current study. Firstly, we may have had insufficient statistical power to detect true but smaller associations between lipids and ischemic stroke in men. However, similar negative findings were described in men in cohorts with a higher incidence of ischemic stroke events, namely the Physician's Health Study (296 ischemic stroke events in 22,071 men followed up for 11.5 years) [14] and the Atherosclerosis Risk in Communities Study (161 incident ischemic stroke events in more than 6,000 men followed up for 10 years) [15]. Secondly, ischemic stroke represents a heterogeneous condition, and the association of lipids with ischemic stroke, if any, may vary according to ischemic stroke subtype. Accordingly, total-C, LDL-C and HDL-C have been shown to be more likely associated with atherothrombotic infarctions than with cardioembolic or lacunar infarctions [11, 12, 28]. Although investigated in a relatively small number of stroke events, we found that lipids were not associated with ischemic strokes when cardioembolic strokes were excluded in the present study. Thirdly, lipids might be associated with ischemic stroke in women but not in men (gender interaction), as suggested by the results of the EUROSTROKE collaborative project for HDL-C [13] and by those of the Atherosclerosis Risk in Communities study for triglycerides and Apo B100, respectively [15]. However, as we examined only men, this hypothesis could not be explored here.

Moreover, our data indicated that Lp(a) was not associated with ischemic stroke. A recent review of observational studies suggested that Lp(a) was an independent predictor of stroke of any type [29], but this review included transient ischemic attack, contrary to our study.

Taken together, previous and current findings suggest that the significantly reduced risk of ischemic stroke among subjects taking statin therapy observed in randomized controlled trials might be due to non-cholesterol or pleiotropic effects, possibly an anti-inflammatory effect [30–32], although this issue has been debated [33].

The strengths of the current study include its prospective design, the use of standardized criteria to define clinical events within the same population and the investigation of a large panel of lipids. However, the study does have some limitations that should be mentioned. As noted above, our study may have lacked statistical power to detect a true but small association of lipids with ischemic stroke events. LDL-C is a heterogeneous group of particles varying in size, and small dense LDL particles have recently been found to be associated with an increased risk of first-ever stroke of thrombotic and hemorrhagic origin [34]. However, small dense LDL particles were not measured in the PRIME Study. No interim examinations were performed in the PRIME Study, so that changes in lipid levels and in lipid-lowering treatment during follow-up were not controlled for. The PRIME Study consisted of healthy middle-aged men, and thus the applicability of the current findings to women and elderly populations needs to be evaluated.

Conclusion

The present population-based study suggests that circulating lipids were weak predictors of ischemic stroke in healthy middle-aged men, contrasting with their robust association with CHD.

Appendix

The PRIME Study Group

The PRIME Study is organized under an agreement between INSERM and the Merck, Sharp and Dohme-Chibret Laboratory, with the following participating laboratories:

- The Strasbourg MONICA Project, Laboratoire d'Épidémiologie et de Santé Publique, EA 3430, Strasbourg, and Université de Strasbourg, Strasbourg, France (D. Arveiler, B. Haas);
- The Toulouse MONICA Project, INSERM, U558, and Department of Epidemiology, Université Paul Sabatier – Toulouse Purpan, Toulouse, France (J. Ferrieres, J.B. Ruidavets);
- The Lille MONICA Project, INSERM, U744, Lille, Institut Pasteur de Lille, Lille, and Université Lille Nord de France, Lille, France (P. Amouyel, M. Montaye);
- Department of Epidemiology and Public Health, Queen's University, Belfast, UK (A. Evans, J. Yarnell, F. Kee);

- Department of Atherosclerosis, INSERM, U545, Lille, Institut Pasteur de Lille, Lille, and Faculté de Médecine, Université Lille Nord de France, Lille, France (G. Luc, J.M. Bard);
- Laboratory of Hematology, INSERM, U626, Hôpital La Timone, Marseille, France (I. Juhan-Vague, P. Morange);
- Laboratory of Endocrinology, INSERM, U563, Toulouse, France (B. Perret);
- Vitamin Research Unit, University of Bern, Bern, Switzerland (F. Gey);
- The Nutrition and Metabolism Group, Center for Public Health, Queen's University, Belfast, UK (J. Woodside, I. Young);
- DNA Bank, INSERM/UPMC, Paris University UMRS 937, Paris, France (F. Cambien);
- The Coordinating Center, Paris-Sud XI University, Villejuif, France (P. Ducimetiere);
- INSERM, Unit 970, Villejuif, and Université Paris V, Paris Cardiovascular Research Center, Paris, France (A. Bingham).

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